(19) RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

PARIS

(11) N° de publication : **2 623 089**
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(21) N° d'enregistrement national : **87 15686**

(51) Int Cl⁴ : A 61 K 9/08, 31/475.

(12) DEMANDE DE BREVET D'INVENTION A1

(22) Date de dépôt : 13 novembre 1987.

(30) Priorité :

(43) Date de la mise à disposition du public de la demande : BOPI « Brevets » n° 20 du 19 mai 1989.

(60) Références à d'autres documents nationaux apparentés :

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(54) Composition pharmaceutique pour l'administration parentérale de navelbine.

(57) La présente invention concerne une composition pharmaceutique pour l'administration parentérale de navelbine, caractérisée en ce qu'elle se présente sous la forme d'une solution aqueuse injectable stable prête à l'emploi.

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La stabilité particulière de la solution injectable selon la présente invention est obtenue au moyen d'une formulation stérile comportant un sel hydrosoluble de navelbine, un agent osmotique, un agent conservateur anti-microbien et de l'eau pour préparation injectable.

De préférence, selon la présente invention, le sel hydrosoluble de navelbine est le di-tartrate. La quantité de principe actif varie bien sûr en fonction de l'état du patient et de l'appréciation du médecin. Elle est en moyenne comprise entre 10 et 50 mg de navelbine base par dose unitaire.

L'agent osmotique de la solution injectable parentérale de la présente invention doit conférer à cette dernière une pression osmotique sensiblement égale à celle du plasma sanguin. Cet agent osmotique comporte, de préférence, une ou plusieurs substances choisies parmi les électrolytes, tels que le chlorure de sodium, les acides aminés, tels que le glycocolle, les sucres, tels que le glucose et/ou les polyols, tels que le mannitol. Ces substances sont utilisées à une concentration de préférence inférieure ou égale à la concentration d'iso-osmose; ainsi le pourcentage de mannitol utilisé est environ égal à 5,07 % (P/V); celui du glucose est environ égal à 5,05 % (P/V).

La stérilité de la composition selon l'invention est assurée grâce au conservateur anti-microbien; ce dernier comporte, de préférence, une ou plusieurs substances choisies parmi les esters ou les sels de l'acide p-hydroxybenzoïque, l'alcool benzylique, les composés mercuriels tels que le mercurothiolate sodique, le chlorobutanol et/ou le phénol ou ses dérivés.

Ces substances peuvent être utilisées seules ou en association entre elles; en tout état de cause, ces substances sont utilisées en quantité efficace et

Exemple

* - Etude analytique de la stabilité de la solution

La composition répondant à la formule suivante

. Navelbine di-tartrate..... 13,85 mg
. Phénol..... 5 mg
. Mannitol..... 37,20 mg
. Eau pour préparations injectables...qsp... 1 ml

a été maintenue dans un récipient de verre à température ambiante et à 40°C, pendant 6 semaines. Une analyse par chromatographie liquide haute performance (CLHP) a été effectuée pour le dosage spécifique de la NAVELBINE.

La méthode CLHP a été la suivante :

- appareil : chromatographe en phase liquide muni d'un détecteur à longueur d'onde variable, fixée ici à 267 nm et d'un injecteur automatique.
- colonne Lichrocart C_{18} - 5 µm (Merck) L = 12 cm
- phase éluante : méthanol 800 ml
  tampon phosphate pH = 7,5 100 ml
  eau 100 ml

On peut remarquer, à partir des figures 1, 2 et 3 qui représentent les chromatogrammes de la solution pour t = 0 et t = 6 semaines à température ambiante et 40°C, que la teneur en navelbine après 6 semaines à 40°C n'est pas inférieure à 97 p.cent de la valeur initiale.

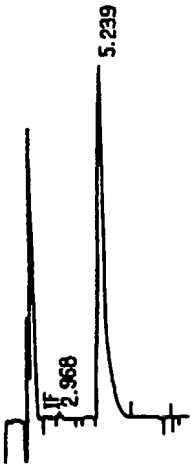

FIG_1

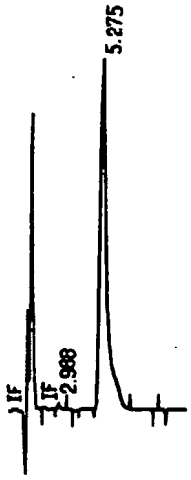

FIG_2

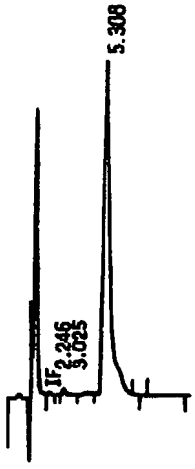

FIG_3

The present invention relates to a pharmaceutical composition for the parenteral administration of navelbine.

Study of the antineoplastic properties of alcaloids of VINCA ROSEA (Apocynaceae family) has enabled the advantageous activities of vinblastine and vincristine to be demonstrated.

Navelbine is an especially effective derivative of vinblastine: it is 5'-noranhydrovinblastine, the synthesis of which is now known (FR-A-2,448,545).

At present, cancer chemotherapy resorts to the combined use of several oncostatics having different toxicities and modes of action. In addition, there are too many instances of chemotherapy ending in failure probably due to the inadequacy or inefficacy of the products employed. Faced with the current upsurge in cases of cancer, the need for oncostatic products is huge.

Thus, the present invention relates to a pharmaceutical composition for the parenteral, and in particular, intravenous, administration of navelbine, which is presented in the form of a stable, ready-for-use injectable solution.

The special stability of the injectable solution according to the present invention is obtained by means of a sterile formulation containing a water-soluble salt of navelbine, an osmotic agent, an antimicrobial preservative agent, and water for injections.

Preferably, according to the present invention, the water-soluble salt of navelbine is the ditartrate. The quantity of active principle naturally varies according to the patient's state and the doctor's assessment. It is between 10 and 50 mg of navelbine base, on average, per unit dose.

The osmotic agent of the parenteral injectable solution of the present invention must impart to the latter an osmotic pressure substantially equal to that of blood plasma. This osmotic agent preferably contains one or more substances chosen from electrolytes such as sodium chloride, amino acids such as glycine, sugars

such as glucose and/or polyols such as mannitol. These substances are used at a concentration preferably below or equal to the isosmotic concentration; thus, the percentage of mannitol used is approximately equal to 5.07% (W/V); that of glucose is approximately equal to 5.05% (W/V).

The sterility of the composition according to the invention is provided by means of the antimicrobial preservative; the latter preferably contains one or more substances chosen from esters or salts of p-hydroxybenzoic acid, benzyl alcohol, mercurial compounds such as sodium mercurothiolate, chlorobutanol and/or phenol or its derivatives.

These substances may be used alone or in combination with one another; in any case, these substances are used in effective and pharmacologically compatible quantities; thus, maximum contents for use are laid down for each of them:

These contents, expressed in W/V, are 0.15% for para-hydroxybenzoic acid derivatives, 1% for benzyl alcohol, 0.01% for mercurial compounds and 0.5% for chlorobutanol or phenol derivatives.

The presence of an antimicrobial agent enables the formulation to be protected from any risk of accidental microbial contamination during its manufacture. In addition, it permits the distribution of the injectable solution in the form of a multidose pack.

In addition, on account of the temperature-sensitivity of navelbine salts in aqueous solution, the sterilization of the solution is procured by filtration through a membrane of porosity 0.2 µm.

By way of example, the composition of the present invention may correspond to the following formula:

Navelbine ditartrate	13.85	mg
Phenol	5	mg
Mannitol	37.20	mg
Water for injections	qs 1	ml

The packaging container may be chosen from plain or brown glass ampoules or glass bottles equipped with

an elastomer stopper.

Tests relating to the stability of the solution according to the present invention were performed and are presented in the example which follows, which is illustrated by Figures 1, 2 and 3 which illustrate the chromatogram of the solution at the following times and temperatures:

Fig. 1 - time 0

Fig. 2 - time = 6 weeks and room temperature

Fig. 3 - time = 6 weeks and temperature = 40°C

Example

Analytical study of the stability of the solution

The composition corresponding to the following formula:

Navelbine ditartrate	13.85 mg
Phenol	5 mg
Mannitol	37.20 mg
Water for injections .....qs	1 ml

was maintained in a glass vessel at room temperature and at 40°C for 6 weeks. An analysis by high performance liquid chromatography (HPLC) was performed for the specific assay of NAVELBINE.

The HPLC method was as follows:

- Apparatus: liquid phase chromatograph equipped with a variable wavelength detector, set in this case at 267 nm, and an automatic injector
- Lichrocart C_{18} - 5 µm (Merck) column: L = 12 cm
- Eluant phase: methanol 800 ml
  phosphate buffer pH 7.5 100 ml
  water 100 ml

It may be noted from Figures 1, 2 and 3, which illustrate the chromatograms of the solution for t = 0 and t = 6 weeks at room temperature and 40°C, that the navelbine content after 6 weeks at 40°C is not less than 97 percent of the initial value.

CLAIMS

1. A pharmaceutical composition for the parenteral administration of navelbine, which is presented in the form of a stable, ready-for-use injectable aqueous solution.

2. The composition as claimed in claim 1, which contains a water-soluble salt of navelbine, an osmotic agent, an antimicrobial preservative agent, and water for injections.

3. The composition as claimed in claim 2, in which the navelbine salt is the ditartrate.

4. The composition as claimed in claim 2 or 3, in which the osmotic agent comprises one or more substances chosen from electrolytes such as sodium chloride, amino acids such as glycine, sugars such as glucose and/or polyols such as mannitol.

5. The composition as claimed in any one of claims 2 to 4, in which the antimicrobial preservative agent comprises one or more substances chosen from esters or salts of p-hydroxybenzoic acid, benzyl alcohol, mercurial compounds such as sodium mercurothiolate, chlorobutanol and/or phenol or its derivatives.

6. The composition as claimed in any one of claims 1 to 5, which corresponds to the following formula:

Navelbine ditartrate	13.85	mg
Phenol	5	mg
Mannitol	37.20	mg
Water for injections .....qs	1	ml

PATENT

PHARMACEUTICAL COMPOSITION FOR THE PARENTERAL ADMINISTRATION OF NAVELBINE

Applicant: PIERRE FABRE MEDICAMENT

ABSTRACT

The present invention relates to a pharmaceutical composition for the parenteral administration of navelbine, which is presented in the form of a stable, ready-for-use injectable aqueous solution.

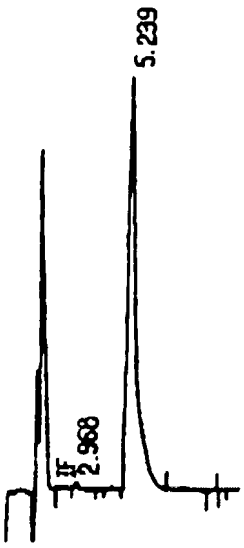

FIG_1

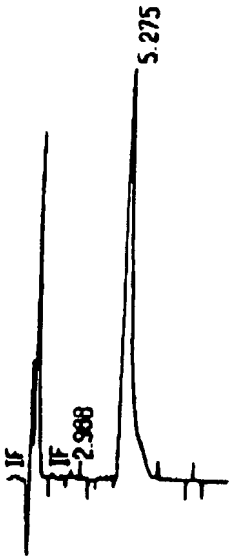

FIG_2

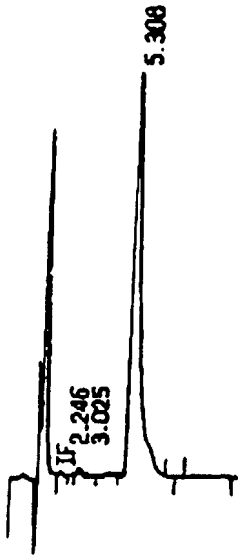

FIG_3